(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030224 A1

(51) International Patent Classification[7]: A61K 31/60, 31/44, 31/216, 31/235, 31/245, A61P 31/12

(21) International Application Number: PCT/EP2004/051551

(22) International Filing Date: 20 July 2004 (20.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03292378.1 26 September 2003 (26.09.2003) EP

(71) Applicant *(for all designated States except US)*: **NICOX S.A.** [FR/FR]; 2455 Routes des Dolines, F-06906 Sophia Antipolis (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOLLA, Manlio** [IT/IT]; Via Monte Popera 11, I-20138 Milano (IT). **SANTUS, Giancarlo** [IT/IT]; Via Zuara 8, I-20146 Milano (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(74) Agent: **BARCHIELLI, Giovanna**; Nicox Research Institute Srl, Via L. Ariosto 21, I-20091 Bresso (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/030224 A1

(54) Title: NITROSYLATED ANALGESIC AND/OR ANTI-INFLAMMATORY DRUGS HAVING ANTIVIRAL ACTIVITY

(57) Abstract: Use for the prevention and/or treatment of viral diseases and/or their complications, of nitroderivatives of general formula (I) or salts or stereoisomers thereof: A-T-Y-ONO_2 (I).

TITLE OF THE INVENTION

NITROSYLATED ANALGESIC AND/OR ANTI-INFLAMMATORY DRUGS HAVING ANTIVIRAL ACTIVITY

******

The present invention relates to the use of drugs for treating viral diseases and/or their complications. More specifically, the present invention relates to the use of nitroderivatives for treatment of influenza, cold and viral infections affecting the cardiovascular system, in particular the heart muscle.

The viral infections are very diffused. The cold and influenza are the common infectious diseases of the respiratory tract caused by different viruses (rhinovirus, influenza viruses). The influenza produces symptoms that are more severe, such as a fever, runny nose, sore throat, cough, headache and muscle aches.

Complications may prolong the illness, some people develop secondary bacterial infections such as otitis media, sinuses, bronchitis and pneumonia.

Vaccination is the best way to avoid contracting influenza and several antiviral drugs can be used to prevent infection and are also helpful in treating people who have influenza.

The drawback of vaccines is that the virus can change each year.

Amantadine and rimantadine are older antiviral drugs that offer protection against influenza type A but not influenza type B. These drugs can cause side effects such as stomach upset, nervousness and sleeplessness. New analogs, oseltamivir and zanamivirm can prevent infection with either influenza virus types.

However, the use of antiviral drugs does not eliminate the risk of complications and these drugs work only if taken in the first day or two of illness. In addition, the virus rapidly develops resistance to them (The Merck Manual of Medical Information, Second Home Edition, Chapter 198, Viral Infections).

Other used compounds are paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs). It has been reported that paracetamol causes damages at hepatic level (hepatic toxicity) and it has been known that the use of NSAIDs is often accompanied by several side effects, mainly at the charge of the gastrointestinal tract. For the cold treatment there are generally no effective antiviral drugs and an effective vaccine has not yet been developed (The Merck Manual of Medical Information, Second Home Edition, Chapter 198, Viral Infections).

The viral infections affecting the heart muscle (myocarditis) are caused by different viruses such as coxsackie, adenovirus, and echovirus. The therapeutic treatment is generally unsatisfactory for the viral myocarditis.

The need was felt to have available compounds active in viral infections, specifically those affecting the cardiovascular system, in particular the heart muscle, and for the prevention and/or treatment of influenza and cold.

It has been surprisingly and unexpectedly found by the Applicant that it is possible to solve the above technical problem with specific nitroderivatives as described hereunder.

Object of the present invention is the use, for the prevention and/or treatment of viral diseases and/or their complications, of nitroderivatives of general formula (I)

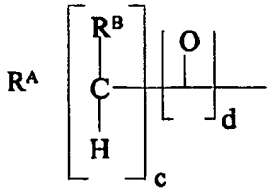
or pharmaceutically acceptable salts or stereoisomers thereof:

$$A\text{-}T\text{-}Y\text{-}ONO_2 \qquad (I)$$

wherein A is the residue of a drug (A-OH or A-H) selected from the group consisting of non-steroidal anti-inflammatory, analgesic and antipyretic drugs and COX-2 inhibitors, in which T = -O-, -NH-, -S-, -CO- or -$(CH_2)_{n1}$OCO- wherein n1 is an integer from 1 to 20;

A is selected from the group consisting of:

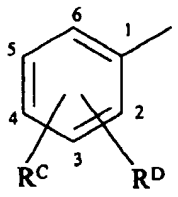
IIa)

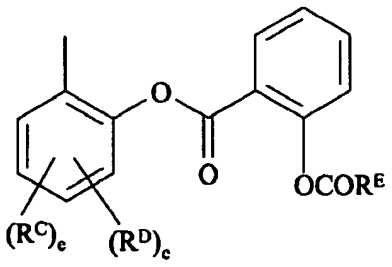


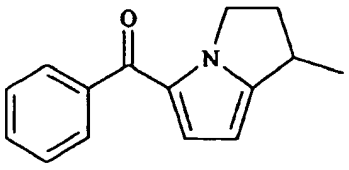
where c and d are independently 0 or 1;

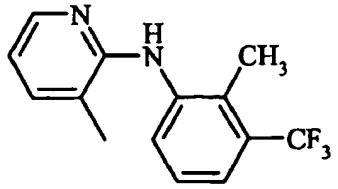
R^B is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl;

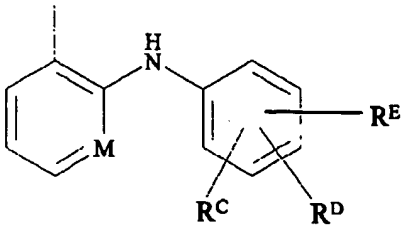
when c is equal to 0 , d is 1, R^A is selected from the group consisting of:

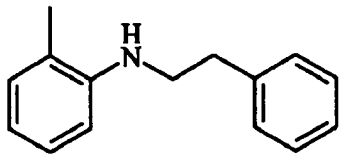












wherein:

R^C is selected from the group consisting of H, halogen, amino, R^ECONH- and $-OCOR^E$;

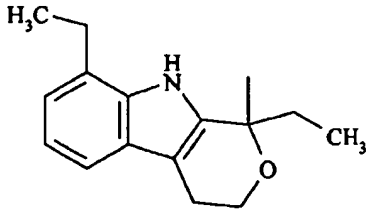
R^D is H, OH, halogen, a linear or branched C_1-C_4 alkyl, a linear or branched C_1-C_4 alkoxyl, trifluoromethyl, amino, mono- or di-(C_1-C_4) alkylamino;

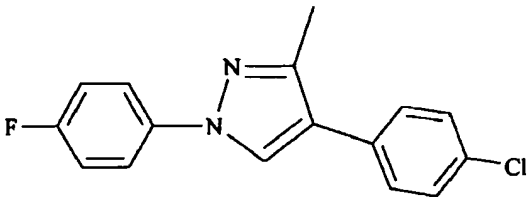
R^E is H and a linear or branched C_1-C_5 alkyl;

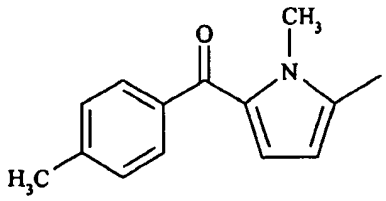
e is 0 or 1;

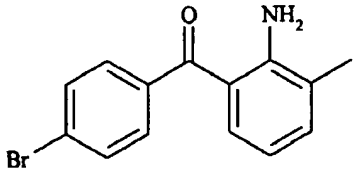
M is carbon or nitrogen atom;

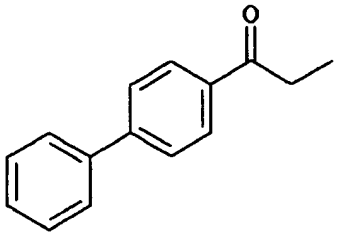
when c is equal to 1, d is equal to 1, R^B is hydrogen, R^A is selected from the group consisting of:

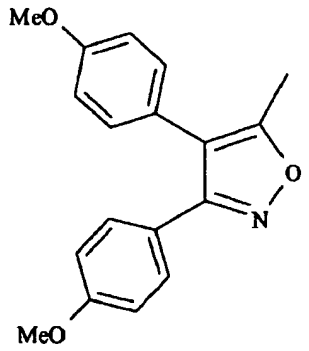


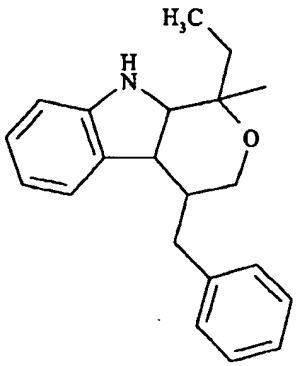


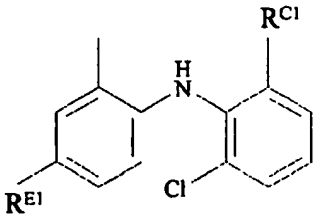


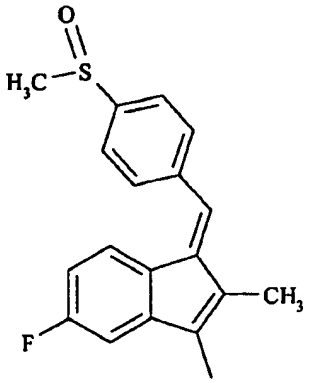


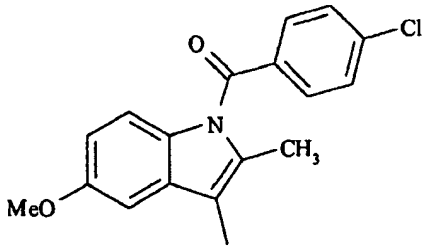






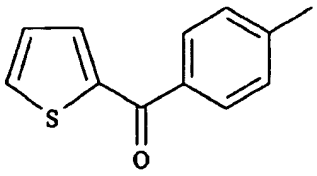


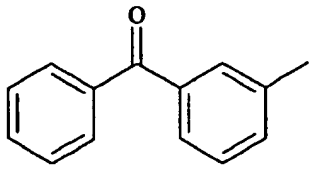


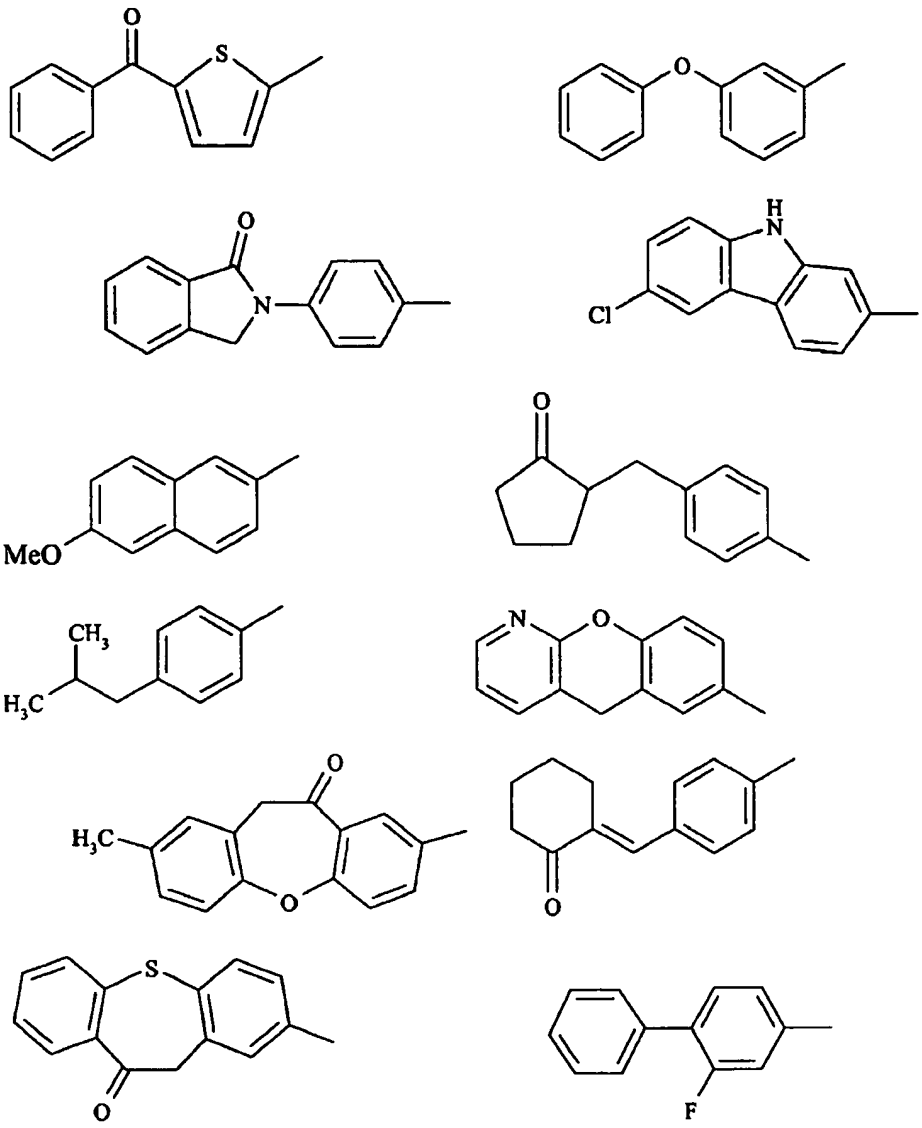


wherein R^{E1} is H or CH_3 and R^{C1} is Cl or F;

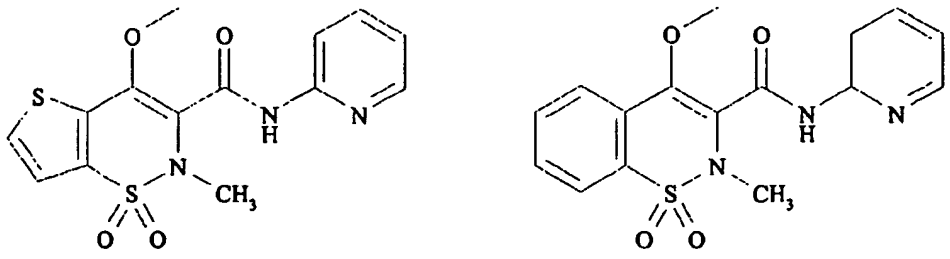
when c is equal to 1, d is equal to 1 and R^B is CH_3, R^A is selected from the group consisting of:

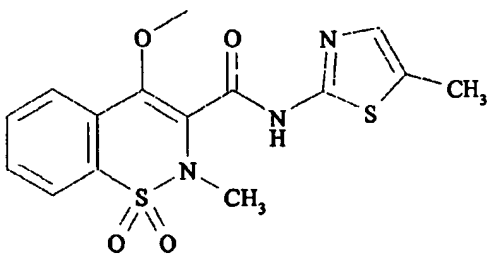


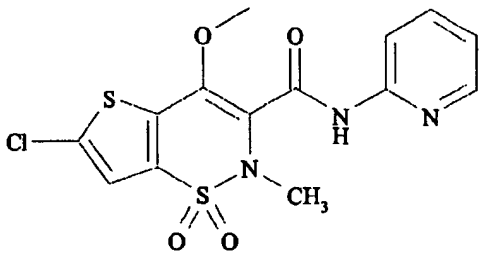


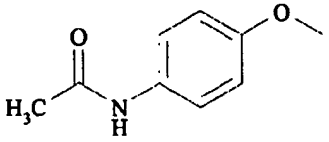


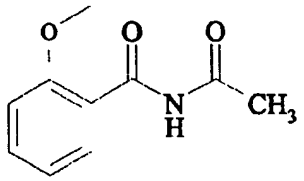
when c is equal to 0, d is equal to 0, R^A is selected from the group consisting of:



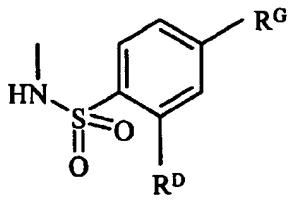








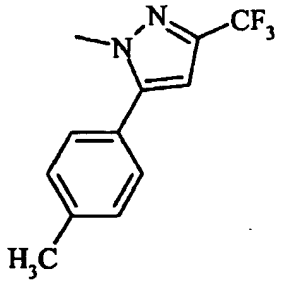
IIb)

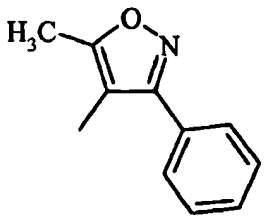


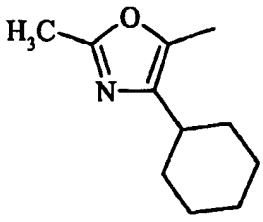
wherein:

R^D is as above defined;

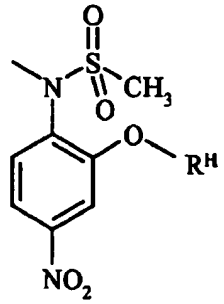
R^G is selected from the group consisting of:





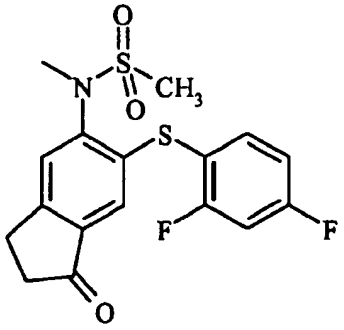


IIc)



wherein R^H is phenyl or cyclohexyl;

IId)

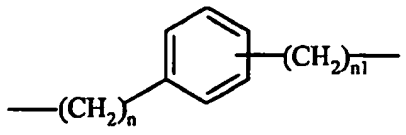


Y is a bivalent radical having the following meaning:

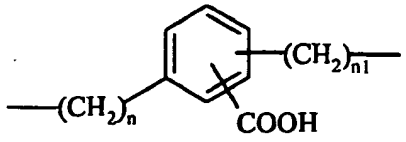
a) - linear or branched C_1-C_{20} alkylene, preferably having from 2 to 5 carbon atoms;

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains R^1, wherein R^1 is linear or branched alkyl with from 1 to 10 carbon atoms, preferably CH_3;

b)

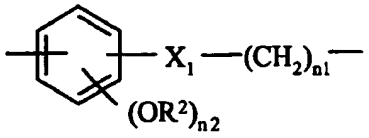


c)



wherein n is an integer from 0 to 20, and n1 is an integer from 1 to 20 as above defined;

d)

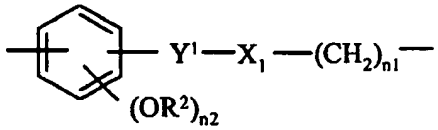


wherein:

n1 is as defined above and n2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

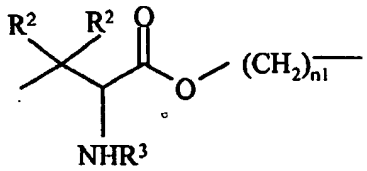


wherein:

n1, n2, R^2 and X_1 are as above defined;

Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n2}-$;

f)

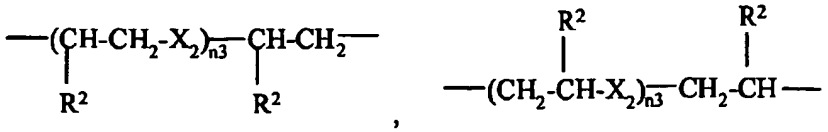


wherein:

n1 and R^2 are as above defined, R^3 is H or $COCH_3$;

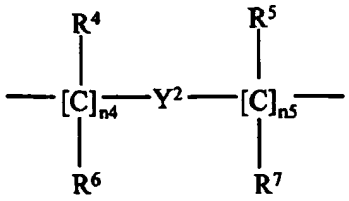
with the proviso that when Y is selected from bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-CH_2$ group;

g)



wherein X_2 is -O- or -S-, n3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as above defined;

h)



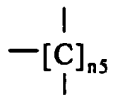
wherein:

n4 is an integer from 0 to 10;

n5 is an integer from 1 to 10;

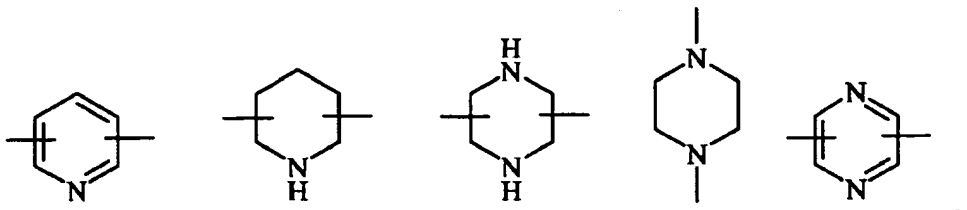
R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^4, R^5, R^6, R^7 are H;

and wherein the $-ONO_2$ group is bound to

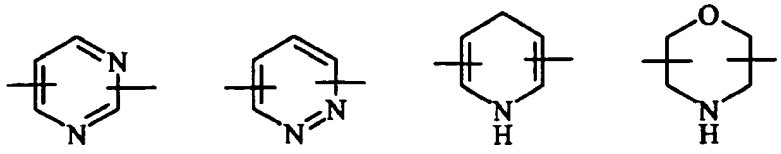


n5 being as defined above;

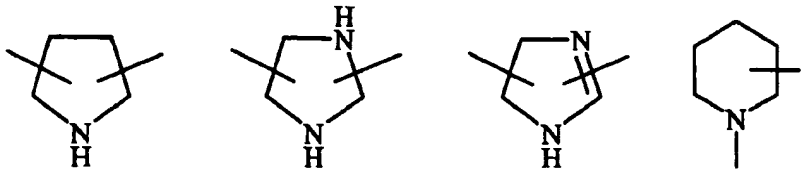
Y^2 is a 5 or 6 member saturated, unsaturated or aromatic heterocyclic ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and selected for example from



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9)



(Y10) (Y11) (Y12) (Y13)

Non limiting examples of non-steroidal anti-inflammatory, analgesic and antipyretic drugs (A-OH or A-H) used in the present invention are:
Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, 5-amino-acetylsalicylic acid, Flunixin, Ketorolac, Tolfenamic acid, Niflumic acid, Mefenamic acid, Meclofenamic acid, Flufenamic acid, Enfenamic acid, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Flurbiprofen, Tenoxicam, Piroxicam, Meloxicam, Lornoxicam, Paracetamol and Salacetamide.

Preferably, the COX-2 inhibitors used in the present invention are selected from the group consisting of:
Celecoxib, Valdecoxib, JTE-522 (Tilmacoxib), COX-189 (Lumiracoxib), Nimesulide, N-(4-nitro-2-cycloexyloxy-phenyl)methanesulfonanilide (NS-398) and N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide (L-745337).

The compounds of formula (I), according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid. Salts with nitric or hydrochloric acid are preferred.

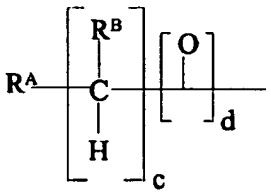
The compounds of the invention which have one or more asymmetric carbon atoms can exist as the optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

The preferred compounds according to the present invention are those wherein:

T = -O-, -NH-, -S- or -CO-;

A is selected from the group consisting of:

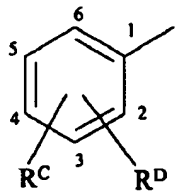
IIa)



where c and d are independently 0 or 1;

R^B is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl;

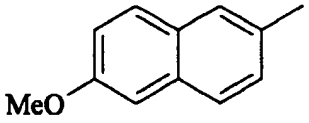
when c is equal to 0 , d is 1, R^A is selected from the group consisting of:

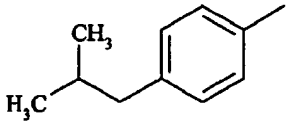


wherein:

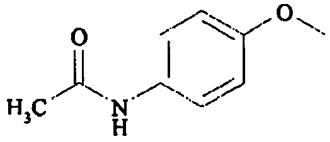
R^C is $-OCOCH_3$ in ortho-position with respect to -CO- and R^D is H;

when c is equal to 1, d is equal to 1 and R^B is CH_3, R^A is selected from the group consisting of:





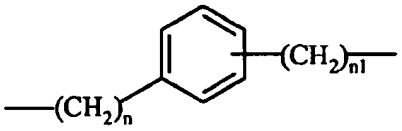
when c is equal to 0, d is equal to 0, R^A is:



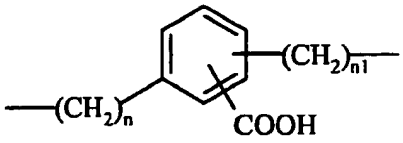
Y is a bivalent radical having the following meaning:

a) linear C_1-C_6 alkylene, preferably having from 3 to 5 carbon atoms;

b)

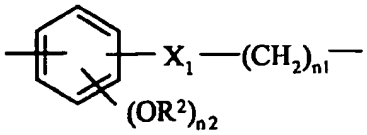


c)



wherein n is an integer from 0 to 5, and n1 is an integer from 1 to 5;

d)

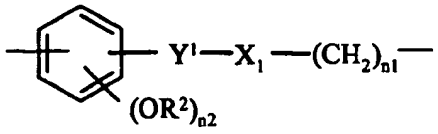


wherein:

n1 is as defined above and n2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

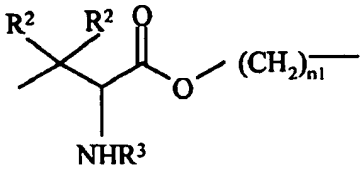


wherein:

n1, n2, R^2 and X_1 are as above defined;

Y^1 is -CH=CH-;

f)

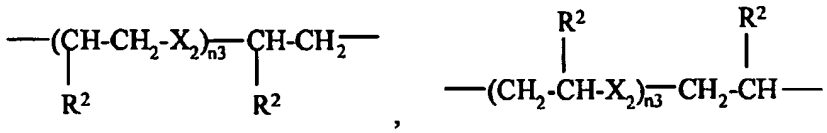


wherein:

n1 and R^2 are as above defined, R^3 is H or $COCH_3$;

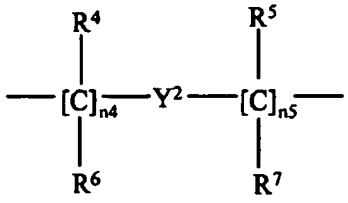
with the proviso that when Y is selected from bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-CH_2$ group;

g)



wherein X_2 is -O- or -S-, n3 is an integer from 1 to 4, preferably 1, R^2 is as above defined;

h)



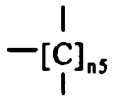
wherein:

n4 is an integer from 0 to 3;

n5 is an integer from 1 to 3;

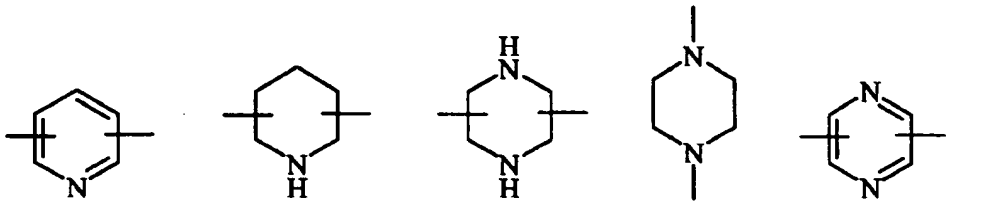
R^4, R^5, R^6, R^7 are the same and are H;

and wherein the $-ONO_2$ group is bound to

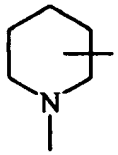


;

Y^2 is a 6 member saturated, unsaturated or aromatic heterocyclic ring, containing one or more atoms of nitrogen and selected for example from

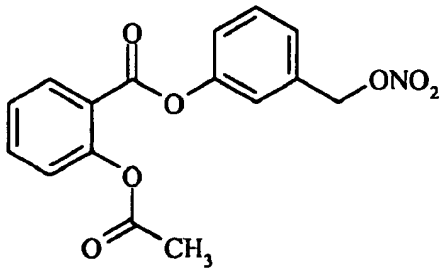


(Y1) (Y2) (Y3) (Y4) (Y5)

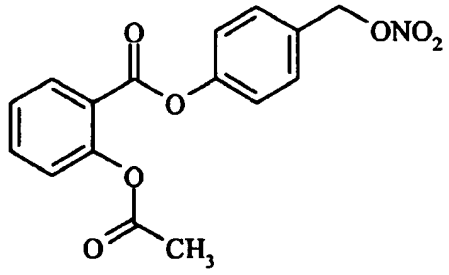


(Y13)

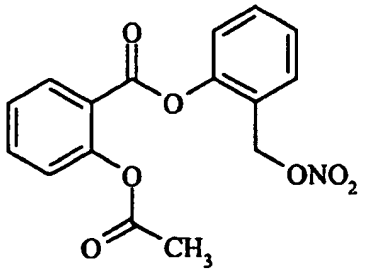
The preferred compounds of formula (I) for the use according to the present invention are the following:



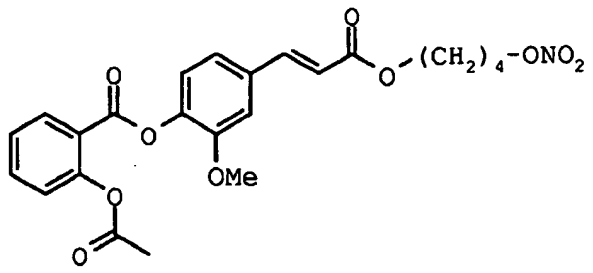
(1)



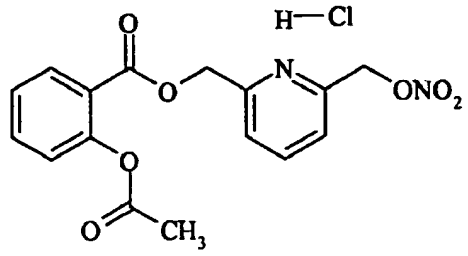
(2)



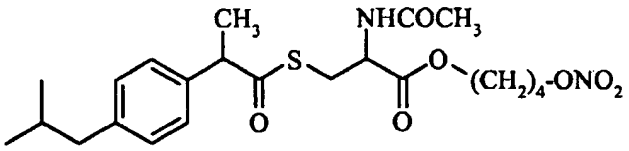
(3)



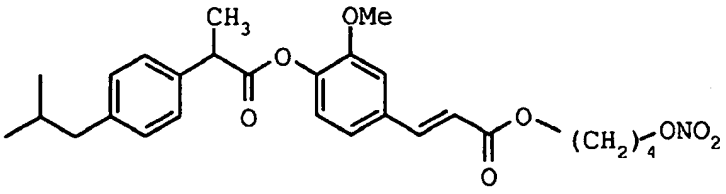
(4)



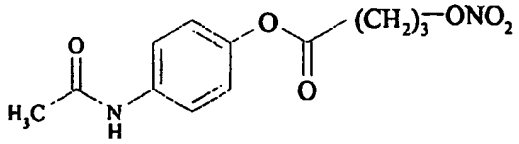
(5)



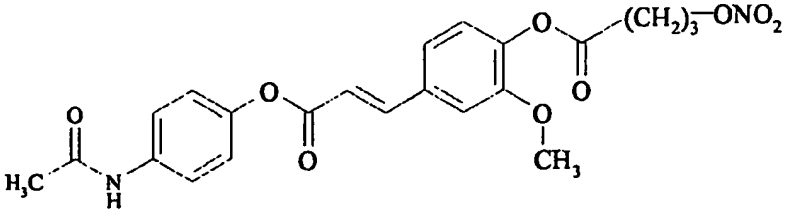
(6)



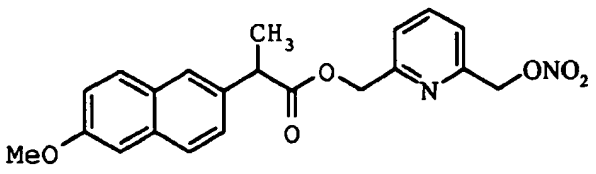
(7)



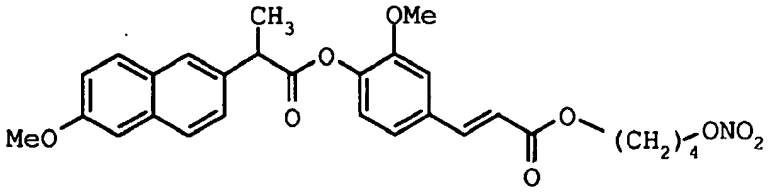
(8)



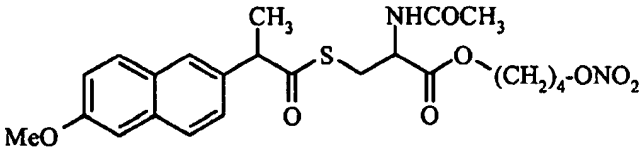
(9)



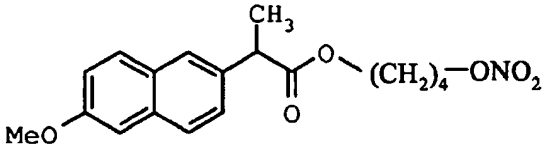
(10)



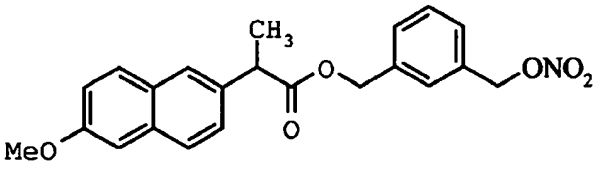
(11)



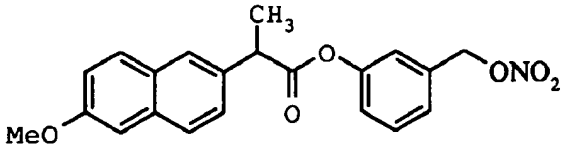
(12)



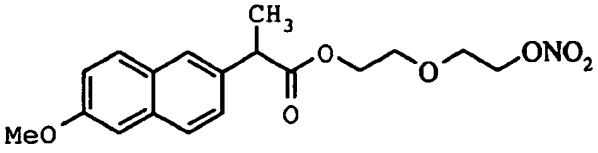
(13)



(14)



(15)



(16)

The preparation of the compounds of formula (I) with the linking group Y of formula h) is described in published PCT application WO 00/51988, pages 28-31, in the name of the Applicant, herein incorporated by reference.

When Y is selected from bivalent radicals mentioned under a)-c) and g), the compounds of formula (I) can be obtained according to U.S. Pat. No. 5,861,426, pages 15-16, in the name of the Applicant, herein incorporated by reference.

The preparation of the compounds of formula (I) with the linking group Y selected from bivalent radicals mentioned under d)-f) is described in published PCT application WO 00/61537, pages 49-59, in the name of the Applicant, herein incorporated by reference.

The preparation of the compounds of formula (I) wherein A is selected from the groups IIb)-IId) is described in not published application PCT/EP03/06502 pages 12-19, in the name of the Applicant, herein incorporated by reference.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topical use according to the techniques well known in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15th Ed.".

The amount on a molar basis of the active principle in said formulations is the same, or lower, with respect to that used as anti-inflammatory, analgesic and antipyretic drug of the corresponding precursor drug.

The daily administrable doses are those of the precursor drugs, or optionally lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following examples are to further illustrate the invention without limiting it.

Example 1

Subconfluent monolayers of MDCK cells are grown Petri dishes (60 mm diameter). Cells are infected with influenza virus A/NWS/33 (MOI=1, multiplicity of infection), and three different concentrations of 4-(acetylamino)phenyl 4-(nitrooxy)butanoate (corresponding to compound (8)) (1 to 100 µM) were tested. Assays were performed in double for each concentration and compared to control non infected dishes.

The viral replication after 24 hours infective cycle (preliminary results at 10 hours are available) was titrated by the plaque infectivity assay, using supernatant dilutions from 10^{-1} a 10^{-8} plus the undiluted supernatant.

Results allowed to assess the antiviral activity of compound (8) in influenza virus A/NWS/33 -infected MDCK cells at 24 hours (and one evidence at 10 hours) post infection.

Virus replication is assessed by infectivity plaque assay expressed as UFP/ml (UFP: unity forming plaque) and the obtained results, reported in Table 1, are expressed as % infectivity vs control.

Table 1

Treatment	Exp 1 (24 h)	Exp 2 (24 h)	Mean % inhibition (24 h)	Exp 3 (10h)
Control infection	100	100	--	100
Compound (8) 100 µM	28.5	50.5	60.5	67
Compound (8) 10 µM	--	67.3	32.7	75
Compound (8) 1 µM	--	72.9	27.1	100

Furthermore, the effect of compound (8) on viral nucleoprotein (NP) expression and distribution in influenza virus A/NWS/33 -infected MDCK after a replication cycle of 10 hours is determined by immunoflurescence assay using a monoclonal antibody specific for NP.

The obtained results, reported in Table 2, are expressed as % of the total.

Table 2

Treatment	Cell number expressing viral NP after 10 hours	Intracellular distribution of NP after 10 hours	
		Nuclear	Nuclear and cytoplasm
Control infection	80% (ECP-)	25%	55%
Compound (8) 100 µM	60% (ECP-)	20%	40%
Compound (8) 10 µM	80% (ECP-)	25%	55%
Compound (8) 1 µM	80% (ECP-)	25%	55%

ECP- = no cytopathic effect induced by the virus

4-(acetylamino)phenyl 4-(nitrooxy)butanoate (compound (8)) showed antiviral effect against human influenza virus (A/NWS/33 type), reducing the viral production with a infective title ratio ranging from 3.5 (Exp 1) to 1.98 (Exp 2), with a mean of 2.74.

Furthermore the anti-viral effect was reduced in a concentration dependent manner, suggesting specificity for the antiviral activity of compound (8).

The treatment with 100 µM of compound (8) for 10 hours after viral infection reduced the viral nucleoprotein expression by 20% of monolayer cells when compared to the control infection plates.

CLAIMS

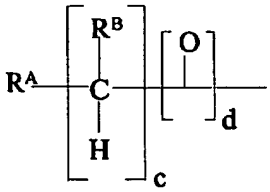
1. Use for the preparation of a medicament for preventing and/or treating viral diseases and/or their complications of compounds, or pharmaceutically acceptable salts or stereoisomers thereof, having the general formula (I):

$$A\text{-}T\text{-}Y\text{-}ONO_2 \qquad (I)$$

wherein A is the residue of a drug (A-OH or A-H) selected from the group consisting of non-steroidal anti-inflammatory, analgesic and antipyretic drugs and COX-2 inhibitors, in which T = -O-, -NH-, -S-, -CO- or -$(CH_2)_{n1}OCO$- wherein n1 is an integer from 1 to 20;

A is selected from the group consisting of:

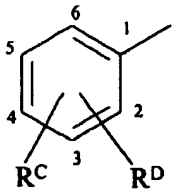
IIa)

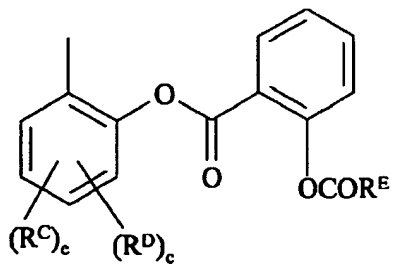


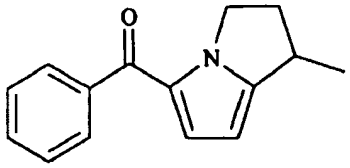
where c and d are independently 0 or 1;

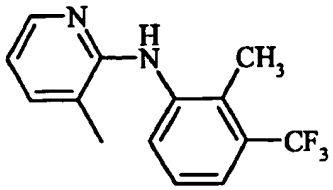
R^B is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl;

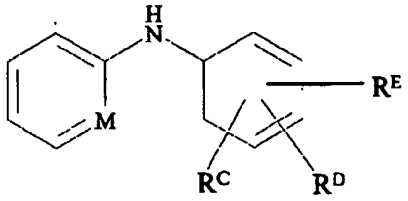
when c is equal to 0 , d is 1, R^A is selected from the group consisting of:

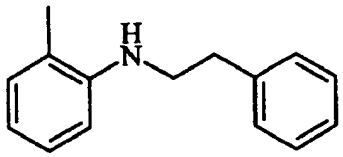












wherein:

R^C is selected from the group consisting of H, halogen, amino, R^ECONH- and $-OCOR^E$;

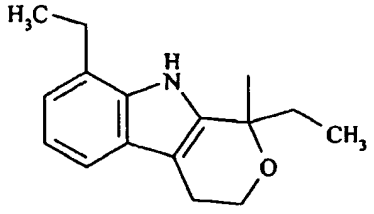
R^D is H, OH, halogen, a linear or branched C_1-C_4 alkyl, a linear or branched C_1-C_4 alkoxyl, trifluoromethyl, amino, mono- or di-(C_1-C_4) alkylamino;

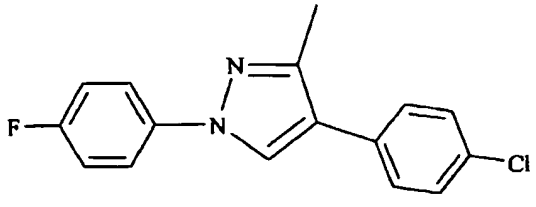
R^E is H and a linear or branched C_1-C_5 alkyl;

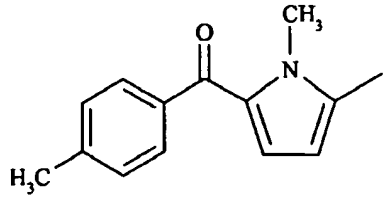
e is 0 or 1;

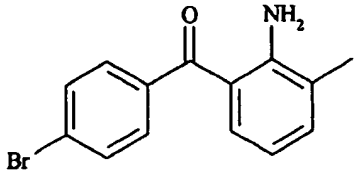
M is carbon or nitrogen atom;

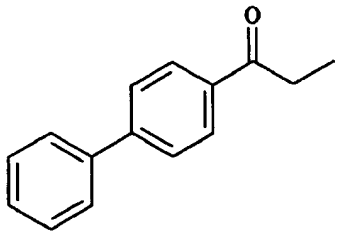
when c is equal to 1, d is equal to 1, R^B is hydrogen, R^A is selected from the group consisting of:

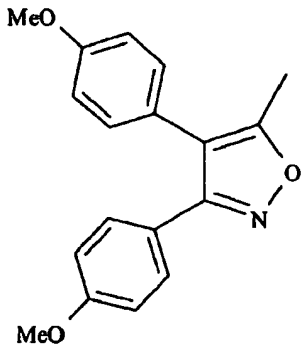


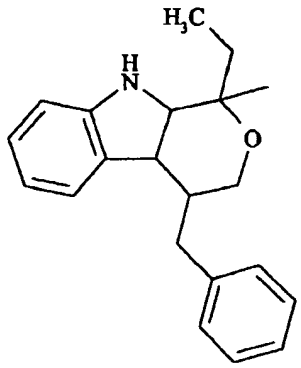


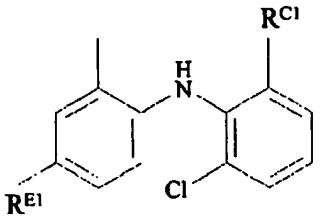


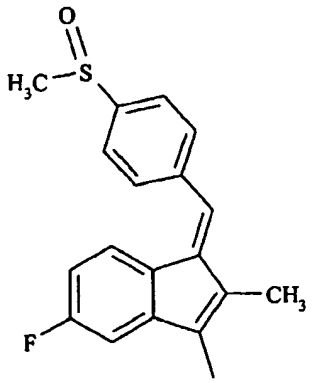


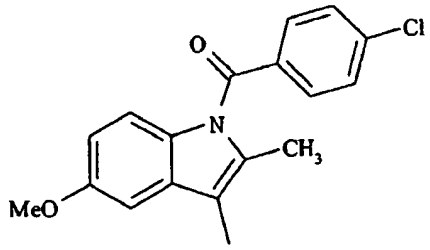






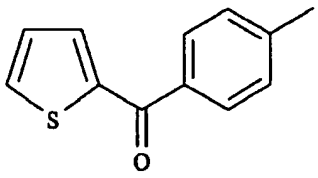


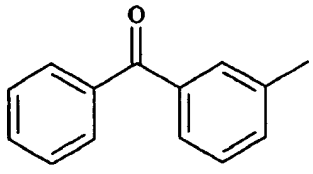


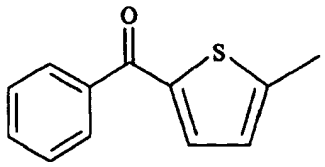
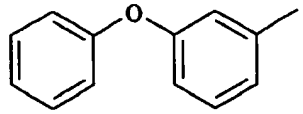
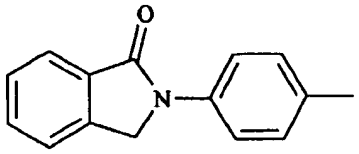
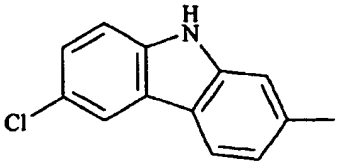
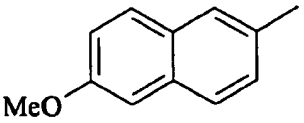
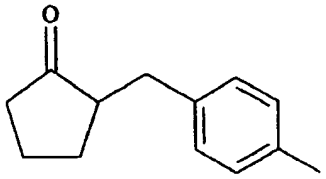
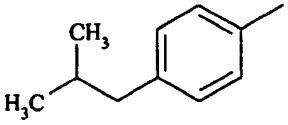
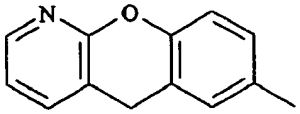
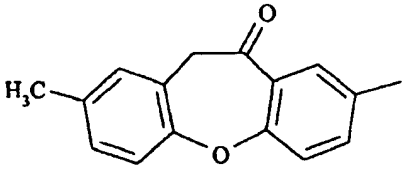
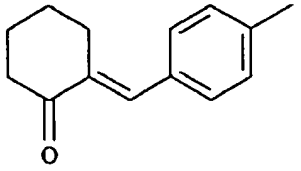
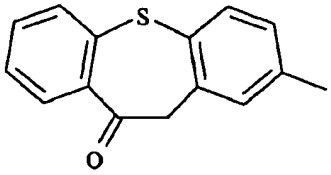
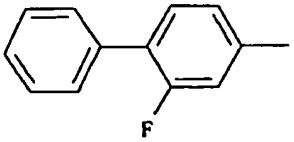


wherein R^{E1} is H or CH_3 and R^{C1} is Cl or F;

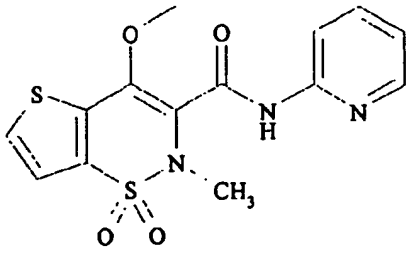
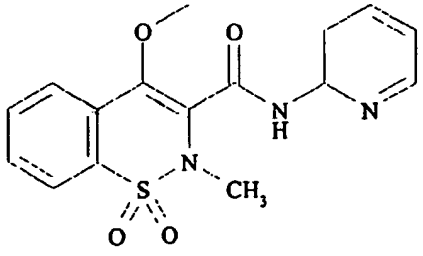
when c is equal to 1, d is equal to 1 and R^B is CH_3, R^A is selected from the group consisting of:

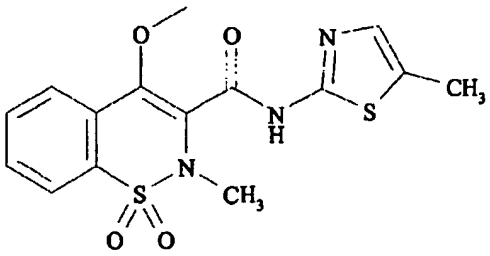
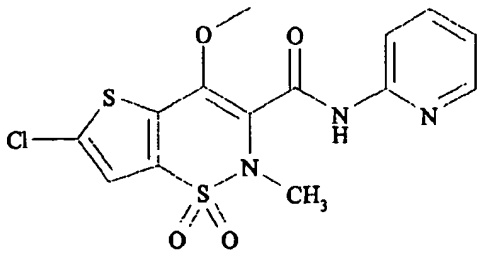
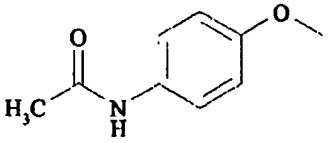
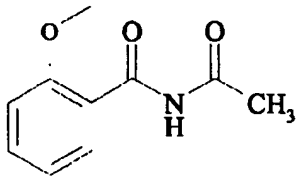




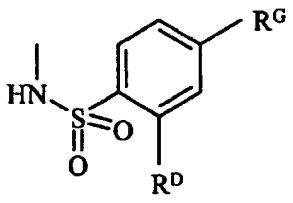













when c is equal to 0, d is equal to 0, R^A is selected from the group consisting of:

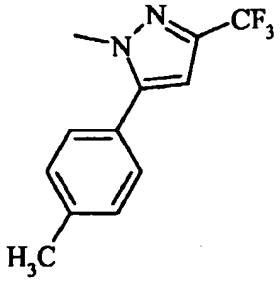
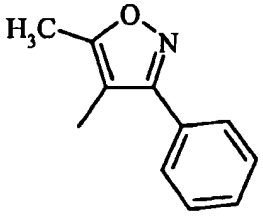
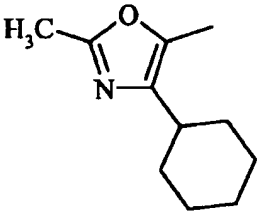
IIb)



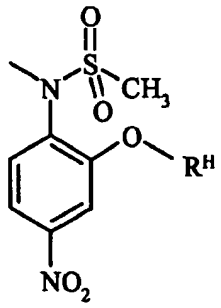
wherein:

R^D is as above defined;

R^G is selected from the group consisting of:

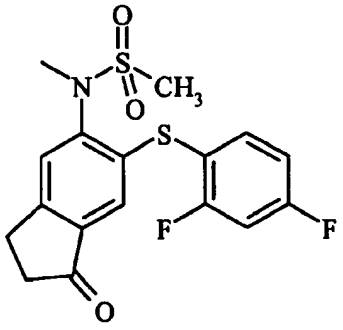




IIc)



wherein R^H is phenyl or cyclohexyl;

IId)

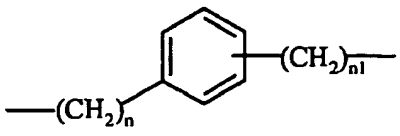


Y is a bivalent radical having the following meaning:

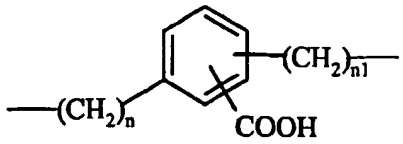
a)

- linear or branched C_1-C_{20} alkylene, preferably having from 2 to 5 carbon atoms;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains R^1, wherein R^1 is linear or branched alkyl with from 1 to 10 carbon atoms, preferably CH_3;

b)

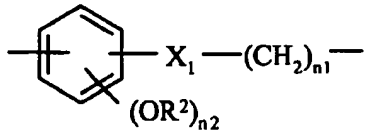


c)



wherein n is an integer from 0 to 20, and n1 is an integer from 1 to 20 as above defined;

d)

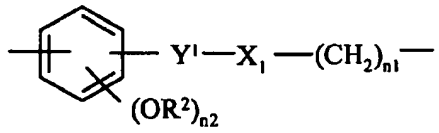


wherein:

n1 is as defined above and n2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

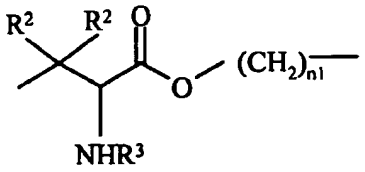


wherein:

n1, n2, R^2 and X_1 are as above defined;

Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n2}-$;

f)

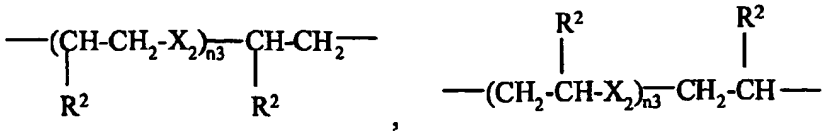


wherein:

n1 and R^2 are as above defined, R^3 is H or $COCH_3$;

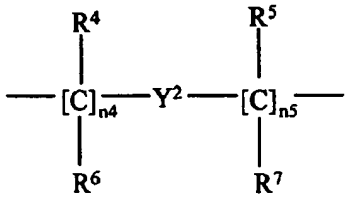
with the proviso that when Y is selected from bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-CH_2$ group;

g)



wherein X_2 is -O- or -S-, n3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as above defined;

h)



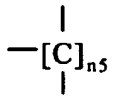
wherein:

n4 is an integer from 0 to 10;

n5 is an integer from 1 to 10;

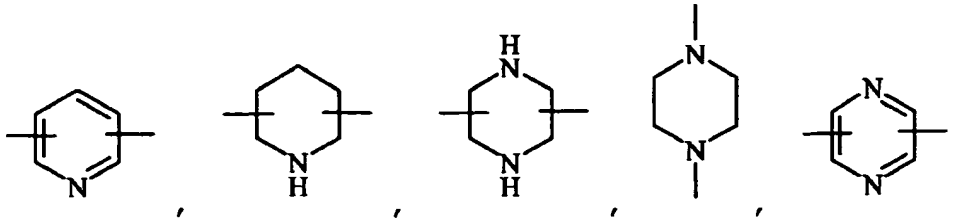
R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^4, R^5, R^6, R^7 are H;

and wherein the $-ONO_2$ group is bound to

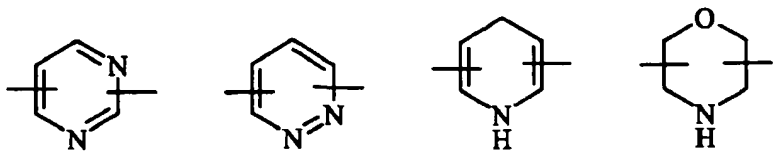


n5 being as defined above;

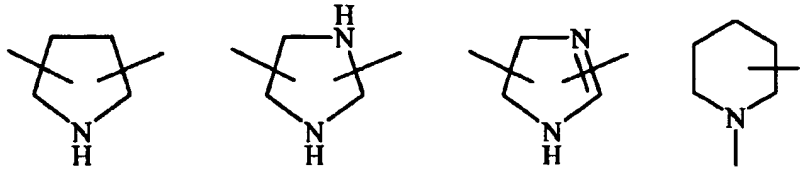
Y^2 is a 5 or 6 member saturated, unsaturated or aromatic heterocyclic ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and selected for example from



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9)



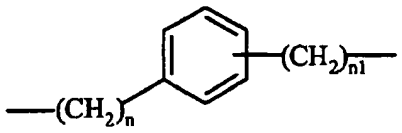
(Y10) (Y11) (Y12) (Y13)

2. Use according to claim 1, wherein the drug (A-OH or A-H) is selected from the group consisting of: Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, 5-amino-acetylsalicylic acid, Flunixin, Ketorolac, Tolfenamic acid, Niflumic acid, Mefenamic acid, Meclofenamic acid, Flufenamic acid, Enfenamic acid, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Flurbiprofen, Tenoxicam, Piroxicam, Meloxicam, Lornoxicam, Paracetamol and Salacetamide, Celecoxib, Valdecoxib, JTE-522 (Tilmacoxib), COX-189 (Lumiracoxib), Nimesulide, N-(4-nitro-2-cycloexyloxy-phenyl)methanesulfonanilide (NS-398) and N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide (L-745337).

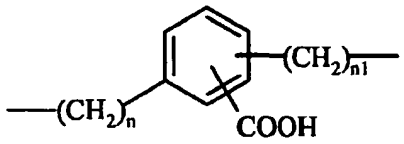
3. Use according to claims 1-2, wherein Y is a bivalent radical having the following meaning:

a) linear C_1-C_6 alkylene, preferably having from 3 to 5 carbon atoms;

b)

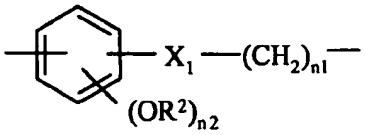


c)



wherein n is an integer from 0 to 5, and n1 is an integer from 1 to 5;

d)

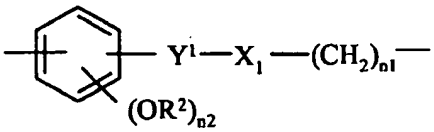


wherein:

n1 is as defined above and n2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

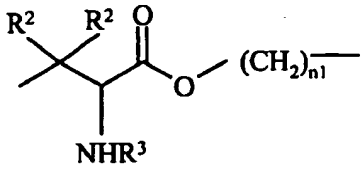


wherein:

n1, n2, R^2 and X_1 are as above defined;

Y^1 is -CH=CH-;

f)

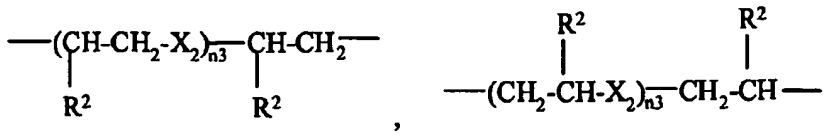


wherein:

n1 and R^2 are as above defined, R^3 is H or $COCH_3$;

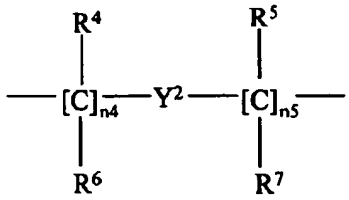
with the proviso that when Y is selected from bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-CH_2$ group;

g)



wherein X_2 is -O- or -S-, n3 is an integer from 1 to 4, preferably 1, R^2 is as above defined;

h)



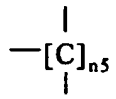
wherein:

n4 is an integer from 0 to 3;

n5 is an integer from 1 to 3;

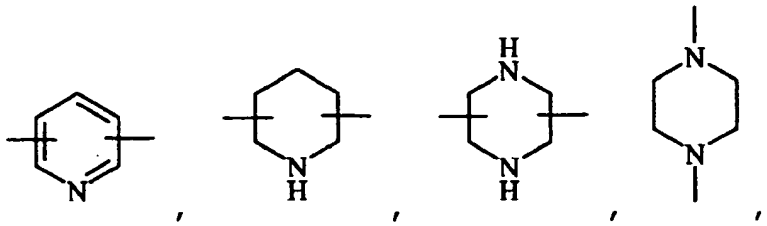
R^4, R^5, R^6, R^7 are the same and are H;

and wherein the $-ONO_2$ group is bound to

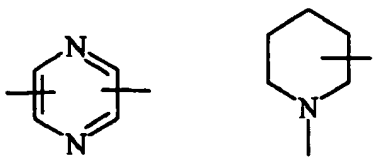


;

Y^2 is a 6 member saturated, unsaturated or aromatic heterocyclic ring, containing one or more atoms of nitrogen and selected for example from



(Y1) (Y2) (Y3) (Y4)

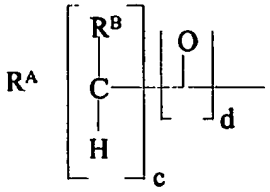


(Y5) (Y13)

4. Use according to claims 1-3, wherein T = -O-, -NH-, -S- or -CO-;

A is selected from the group consisting of:

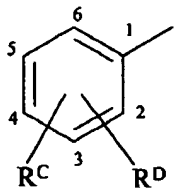
IIa)



where c and d are independently 0 or 1;

R^B is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl;

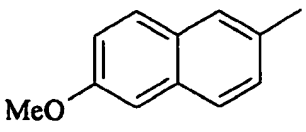
when c is equal to 0 , d is 1, R^A is selected from the group consisting of:

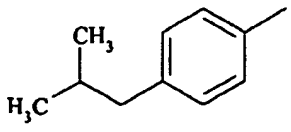


wherein:

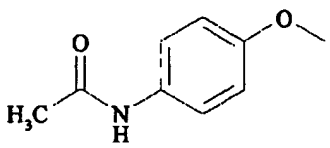
R^C is $-OCOCH_3$ in ortho-position with respect to -CO- and R^D is H;

when c is equal to 1, d is equal to 1 and R^B is CH_3, R^A is selected from the group consisting of:



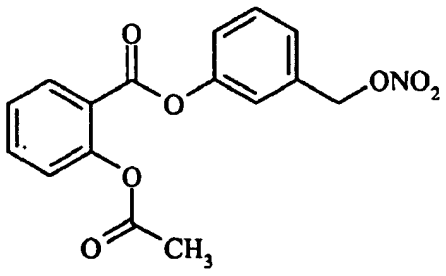


when c is equal to 0, d is equal to 0, R^A is:

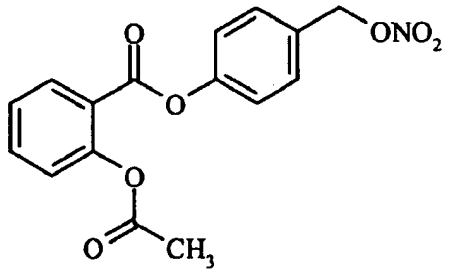


5. Use according to claims 1-4, wherein the non-steroidal anti-inflammatory, analgesic and antipyretic drugs are selected from the group consisting of: Aspirin, Naproxen, Ibuprofen and Paracetamol.

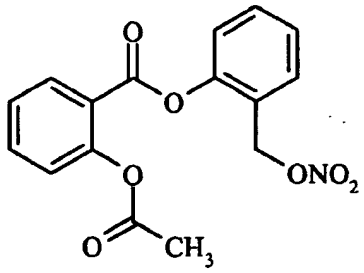
6. Use according to claims 1-5, wherein the preferred compounds of formula (I) are the following:



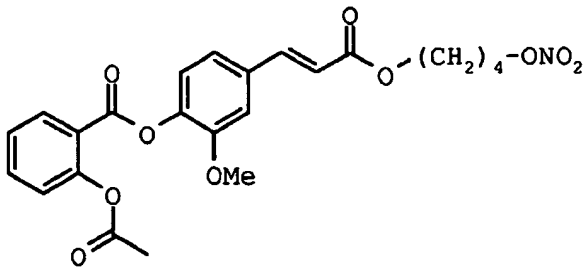
(1)



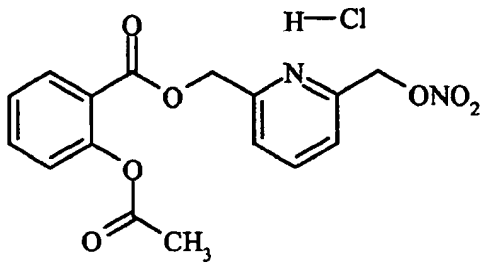
(2)



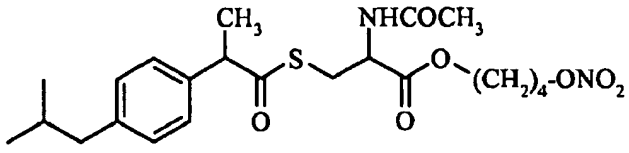
(3)



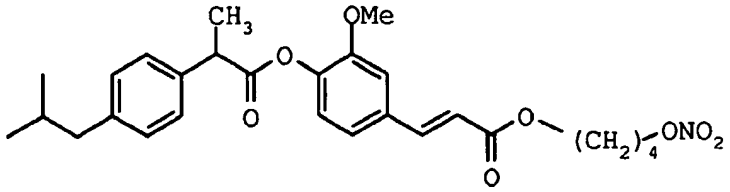
(4)



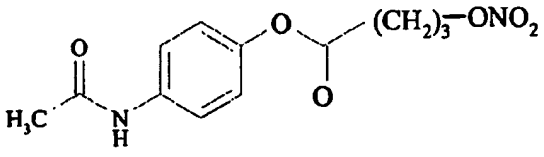
(5)



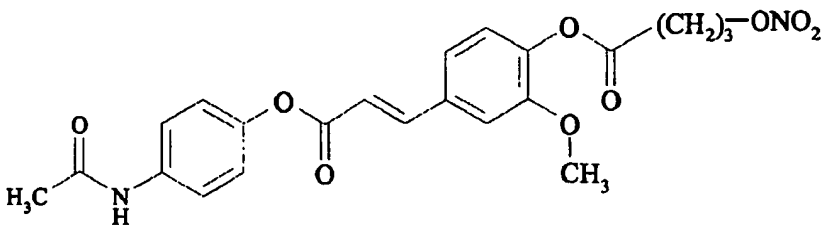
(6)



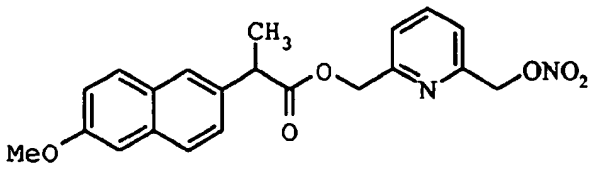
(7)



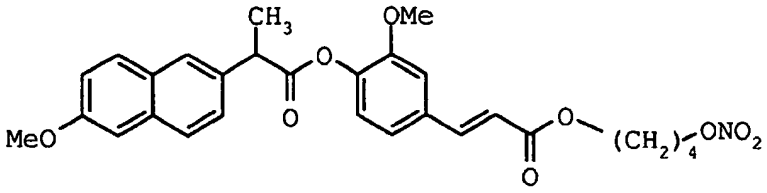
(8)



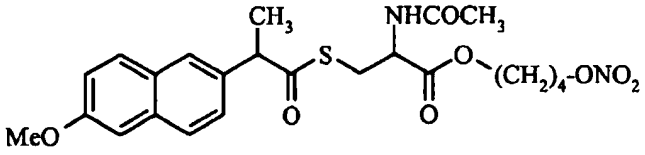
(9)



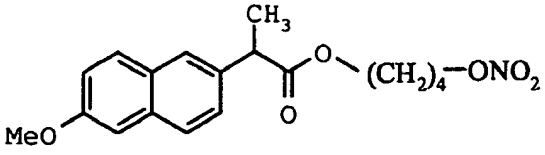
(10)



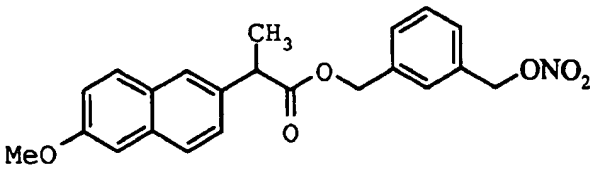
(11)



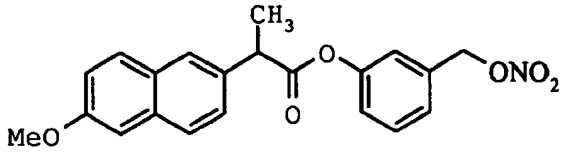
(12)



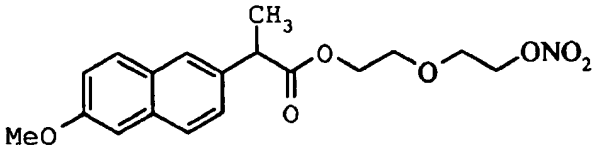
(13)



(14)



(15)



(16)

7. Use of compounds or salts or stereoisomers thereof according to claims 1-6, for the preparation of a medicament for preventing and/or treating of influenza, cold and viral infections affecting the cardiovascular system and/or their complications.

8. Use according to claims 1-7, wherein the compounds or salts or stereoisomers thereof are used in the corresponding pharmaceutical formulations for parenteral, oral and topical use.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051551

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/60 A61K31/44 A61K31/216 A61K31/235 A61K31/245
A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, MEDLINE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/013432 A (GARVEY DAVID S ; LETTS L GORDON (US); NITROMED INC (US)) 20 February 2003 (2003-02-20) page 11, line 28 - page 12, line 2 page 23, line 5 - page 24, line 10	1-5,7,8
X	WO 01/45703 A (FANG XINQIN ; GARVEY DAVID S (US); LETTS L GORDON (US); NITROMED INC () 28 June 2001 (2001-06-28) page 99, lines 8,23 page 20, formula I	1-3
Y	US 5 861 426 A (DEL SOLDATO PIERO ET AL) 19 January 1999 (1999-01-19) claims 1-40	1-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2004	21/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Young, A

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051551

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 219 306 A (NICOX SA) 3 July 2002 (2002-07-03) claims 1-10	1-8
Y	FIORUCCI S ET AL: "A NO-releasing derivative of acetaminophen spares the liver by acting at several checkpoints in the Fas pathway" BRITISH JOURNAL OF PHARMACOLOGY 2002 UNITED KINGDOM, vol. 135, no. 3, 2002, pages 589-599, XP008036060 ISSN: 0007-1188 page 598, right-hand column, paragraph 2 abstract	1-8
Y	KHALILI P ET AL: "Biochemical and pharmacokinetic evaluation of a novel pyrimidine nucleoside nitric oxide donor as a potential anticancer/antiviral agent" EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 2003 NETHERLANDS, vol. 19, no. 4, 2003, pages 305-313, XP008036045 ISSN: 0928-0987 abstract	1-8
Y	DE CLERCQ E ET AL: "5-Nitro-2'-deoxyuridine and 5-nitro-2'-deoxyuridine 5'-monophosphate: Antiviral activity and inhibition of thymidylate synthetase in vivo" MOLECULAR PHARMACOLOGY 1978 UNITED STATES, vol. 14, no. 3, 1978, pages 422-430, XP008036061 abstract	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/051551

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03013432 A	20-02-2003	CA	2453433 A1	20-02-2003
		EP	1414432 A2	06-05-2004
		WO	03013432 A2	20-02-2003
		US	2004152753 A1	05-08-2004
WO 0145703 A	28-06-2001	AU	2592801 A	03-07-2001
		BR	0017037 A	10-06-2003
		CA	2393724 A1	28-06-2001
		CN	1434712 T	06-08-2003
		EP	1246621 A1	09-10-2002
		JP	2003523958 T	12-08-2003
		NZ	519781 A	30-04-2004
		WO	0145703 A1	28-06-2001
		US	2003220228 A1	27-11-2003
		US	2001041726 A1	15-11-2001
		ZA	200205707 A	11-11-2003
US 5861426 A	19-01-1999	IT	1269735 B	15-04-1997
		IT	1274609 B	18-07-1997
		AU	702662 B2	25-02-1999
		AU	2215695 A	29-11-1995
		BR	9507634 A	23-09-1997
		DE	69512232 D1	21-10-1999
		DE	69512232 T2	24-02-2000
		DK	759899 T3	20-12-1999
		EP	0759899 A1	05-03-1997
		GR	3032078 T3	31-03-2000
		JP	9512798 T	22-12-1997
		RU	2145595 C1	20-02-2000
		SI	759899 T1	31-12-1999
		AT	168986 T	15-08-1998
		AT	184589 T	15-10-1999
		AU	678063 B2	15-05-1997
		AU	7809294 A	01-05-1995
		BR	9407749 A	12-02-1997
		CA	2173582 A1	13-04-1995
		CA	2190087 A1	16-11-1995
		DE	69412109 D1	03-09-1998
		DE	69412109 T2	21-01-1999
		DK	722434 T3	16-11-1998
		WO	9509831 A1	13-04-1995
		WO	9530641 A1	16-11-1995
		EP	0722434 A1	24-07-1996
		ES	2120070 T3	16-10-1998
		ES	2139199 T3	01-02-2000
		HU	74446 A2	30-12-1996
		HU	75961 A2	28-05-1997
		JP	9503214 T	31-03-1997
		RU	2136653 C1	10-09-1999
		SI	722434 T1	31-12-1998
		US	5700947 A	23-12-1997
		US	5780495 A	14-07-1998
EP 1219306 A	03-07-2002	EP	1219306 A1	03-07-2002
		WO	02053188 A1	11-07-2002
		EP	1347782 A1	01-10-2003
		JP	2004517116 T	10-06-2004
		US	2004072798 A1	15-04-2004